UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,550	04/07/2005	Takayuki Kotani	9694-000020/NP	7632

27572 7590 03/09/2010

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 828
BLOOMFIELD HILLS, MI 48303

EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
03/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,550	KOTANI ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/09/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 7-9* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Amendment filed 10/09/2009 is acknowledged. Claims 1,4,7,8,9 are pending.

Claim 9 remain withdrawn from consideration.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1,4,7,8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The reasons rejection is applied for the following reasons as applied to claim 1; consequently, claims 4, 7,8 are rejected for the same reasons.

A. Claim 1: The claims address generating QSAR relationship for a compound generated from a plurality of molecules. However, the claim does not address how the compound is being generated. Rather, the claim is directed to determining QSAR for a set of points generated from a plurality of known compounds. Although the claims address quantitative structure-activity relationship "of a chemical compound", the method steps in fact address cumulation of points obtained by

superimposition of coordinates of vaguely related chemical entities. That's why Examiner is questioning what is "the compound" addressed in the claims.

Response to arguments

Applicant argues that the claim does not purport to cover the actual fabrication of the chemical compound, and thus the steps one would employ to manufacture the actual molecule are not encompassed by claim 1. Examiner fully agrees that the claims are not directed to fabrication of the chemical compound. The issue, however, is that it is not clear how a quantitative structure-activity relationship can be obtained for a set of points rather than a compound. Although the claims address quantitative structure-activity relationship "of a chemical compound", the method steps in fact address cumulation of points obtained by superimposition of coordinates of vaguely related chemical entities. That's why Examiner is questioning what is "the compound" addressed in the claims. can be obtained for a set of points rather than a compound. generated from the claims address generating QSAR relationship for a compound generated from a plurality of molecules

B. The claims are amended to address "chemical compound derived from a plurality of molecules each having a related biological activity" The metes and bounds of the term "related pharmacological activity" is not clear and is not defined in specification. For example, will treating blood circulation disorders be considered to be a related pharmacological activity? And if so, to combine such "unrelated" compounds as heparin, blood coagulation proteins, iron salts, and aspirin? Note that applicant in the response to rejection "I" (p. 11, last paragraph of the response) specifically states

that "there is not a strict structural requirement for each of plurality of molecules being superposed".

Further, what will be the merit of clustering together coordinates of atoms of such unrelated compounds per step B of the method?

Furthermore, what will be the significance of generating a new compound out of coordinates of atoms of such unrelated compounds. Note that the examples in specification are limited to structurally related sets of steroids or Cox inhibitors.

Response to arguments

Applicant submits that replacing term "pharmacological activity" with "biological activity" overcomes the rejection. Examiner maintains that the issue of the rejection remains the same as applied to the term "biological activity".

C. Step C: The claim addresses calculating interaction between atoms and represented points. The latter, "represented points", is a calculated 3D coordinates in virtual space. It is not clear how atoms may have "interaction" with such "represented points". In particular, it is not clear how an atom and a "represented point" may have such interactions as steric, electrostatic, or hydrophobic.

Applicant explains, in the response of 10/09/2009 that the claimed method "does not care about the atom type being substituted. Thus, nominal values can be given to the represented point". In response, if it is a random value is to be given to a 3D coordinate in virtual space, then it is not clear what are the "interactions" that are being calculated, what relevance they have to true "steric, electrostatic, and hydroiphobic" interactions, and how such abstract interactions are related to predicting activity which follows in subsequent steps.

Further, as stated in the previous Office action, inasmuch as the claims encompass clustering of atoms of potentially structurally unrelated compounds, such clustering may be a result of combining atoms of different nature (e.g., carbon and nitrogen), and thus even if "represented point" have been inheriting property of originating atoms (which it is not), the resulting "representation" would bear some indefinite characteristics.

D. Step C: The step requires calculation of interactions between the atoms of clustered molecules. Is it every and each atom of each molecule? If yes, then it is not clear how all the atoms interact with a lesser number of "represented points" – which is lesser because B1-B5 clustering steps terminate as soon as predetermined distance threshold is exceeded. If not all the atoms, then it is not clear what portion of atoms is to be considered; also, then it is not clear how each atom is assigned an activity value per step E.

Response to arguments

in response to this rejection, applicant addresses different issue and does not answer the questions asked about vagueness of interaction:

Is it every and each atom of each molecule?

If yes, then it is not clear how all the atoms interact with a lesser number of "represented points"?

If not , then it is not clear what portion of atoms is to be considered?

How each atom is assigned an activity value per step E

Instead, applicant informs that "interactions are calculated by treating all points the same", and "while such interactions would not necessarily correlate to actual energy terms (as would be the case in interaction between actual atoms in a molecule), the interaction values still provide a relative measure that the applicants method is able to use" (p. 17 of the response)

E. Claim 1, process D: process D is directed to correlating statistical analysis of interactions between atoms and "represented points". As addressed in the preceding paragraph, it is not clear what is the significance of interaction between an atoms and an arbitrary "represented point".

Further, it is not clear how and what plurality of "correlation coefficients" is being calculated, and what "activity predicting formula" is being formed.

Response to arguments

Applicant suggests that the basis of rejection is adequately addressed by the description of the overview of the method presented in the response. The general description of the method presented in the response does not seem to address the issues with the claim language addressed in the instant rejection. Please clarify.

F. Step D: "calculating correlation with said pharmacological activity". As addressed above a "related pharmacological activity" is a vague term, and it is not clear how the calculating of correlation of interaction of "represented points" and atoms of possibly structurally unrelated compounds with broadly addressed "related activity" is being carried out.

Response to arguments

Applicant submits that the term "pharmacological activity" was amended. However, even if this term was replaced at the beginning of the claim, it s still present in the description of step D. Furthermore, replacement of "pharmacological" with a broader term "biological" does not change the issue.

G. Further, step D recites "forming an activity prediction formula" . The specification does not provide support anywhere for a method comprising forming an activity prediction formula, and thus the claim is not being commensurate in scope with the specification. Specification does not teach any activity prediction formula; the only formula addressed is the one on Fig. 3. However, neither the activity shown in the table of Fig. 3, nor the terms used in the formula are explained in the specification. It seems from the specification, p. 30, first paragraph, that Fig. 3 addresses function evaluating interactions between the represented point and the molecules, rather than "activity prediction formula" addressed in the claim. Also, as written, it is unclear whether said "forming an activity prediction formula" is an active method step to be practiced in addition to step of "calculating correlation with said pharmacological activity".

Response to arguments

Applicant discusses concepts discussed in the specification. Examiner maintains that the specification does not teach any activity prediction formula.

H. Step E: It is not clear how activity value for each atom of plurality of different molecules – presumably having different amount of atoms – is overlayed on a region (which region?) of one compound (which is the derived chemical compound)

Response to arguments

Applicant submits that claim was amended to recite "at least one" of the plurality of molecules. Even though Examined disagrees that such amendment would have resolved the issue, the main point is that no such amendment was made.

Claim Rejections - 35 USC § 112, first paragraph (written description).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1,4,7,8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is applied for the following reasons:

A. Claims 1,4 introduce new matter as they use the phrase "assigning activity prediction value to each atom". There is no disclosure in the specification of "assigning

activity prediction value to each atom" and there is no guidance on how to practice the claimed method as instantly claimed.

Applicant previously argued that one of ordinary skill in the art could be guided by the teachings of Cramer et al., U.S. Patent No. 5,025,388, to plot the activity prediction values. First, the Cramer patent is not incorporated by reference, and thus does not provide written description for the instant invention. Second, as follows from applicant's discussion, p. 17 of the response of 03/19/2009, Fig. 3 demonstrates CoMFA data table, and equation derived therefrom. However, applicant highlights the different nature of the "represented point" as compared to "probe atoms" of CoMFA (p. 13 of the response of 03/19/2009):

> Instead of using a probe atom, the present application directs the use of a represented point, which is a different point of reference within the molecule being analyzed and is determined using a different method when compared to traditional CoMFA

Response to arguments

Applicant directs to paragraphs [0009] and [0121]. None of these paragraphs demonstrate assigning activity value to each atom. Furthermore, paragraph [0009] describes CoMFA method from which the instant invention distinguishes itself. Further, applicant directs to Fig. 3. Said Figure does not describe assigning activity value to each atom, rather it addresses "points" which are 3D coordinates in virtualm space. Furthermore, as for paragraph [0009], Fig. 3 describes CoMFA method from which the instant invention distinguishes itself.

B. The claims are amended to address method for generating a three-dimensional quantitative structure-activity relationship for a chemical compound derived from a plurality of molecules each having a related biological activity. Such amendment represents a new matter as specification does not address chemical compound derived from a plurality of molecules each having a related biological activity. At best, in one instance, Summary section of specification, p. 15, lines 10-15, addresses the intention of the invention (not supported elsewhere in specification) for a method of extracting and displaying characteristics of a compound based on the atomic coordinates of plural molecules which are superposed in a virtual space. "Compound based on the atomic coordinates" is viewed as *in silico* representation based on the atomic coordinates as opposed to chemical compound derived from other molecules as now addressed in the claims. Further, with regard to said chemical compound, the claims now address displaying said activity prediction values of each atom of said plurality of molecules overlayed on a region of said compound. This is not supported by specification as well.

The inventor must be able to describe the item to be patented with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique method that makes it worthy of patent protection. The reader can certainly appreciate the goal but establishing goals does not make a patent. As the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171

(Fed. Cir.1993). To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cat*h, 935 F.3d at 1563; *see also Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"). There is no demonstration in the specification that applicants generated any chemical compound derived from a plurality of molecules each having a related biological activity. Similarly to *In re Wilde*r, 736 F.2d 1516 (Fed. Cir. 1984), *cert. denie*d, 469 U.S. 1209 (1985) the specification did "little more than outline] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate." Section 112, first paragraph, requires the patentee to "show that an invention is complete by disclosure of substantially detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the invention. As was mentioned in the rejection, the Court of Appeals for the Federal Circuit stated in a case involving similar issues, an inadequate patent description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived." *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir.1993).

Response to arguments

Applicant submits that "the basis of this rejection is the same as 2H above. Applicants have amended the claim as discussed above and thus believe that this rejection is now moot". The rejection 2H is maintained (see above). The instant rejection is revised to address biological, rather than pharmacological, activity.

C. Step D recites "forming an activity prediction formula" . The specification does not provide support anywhere for a method comprising forming an activity prediction formula, and thus the claim is not being commensurate in scope with the specification. As written, it is unclear whether said "forming an activity prediction formula" is an active method step to be practiced in addition to step of "calculating correlation with said biological activity".

Response to arguments

Applicant submits that "this issue has been addressed above in connection with issues 2G and Rejection A of this part." In response, both of the said rejections have been maintained (see above).

Claim Rejections - 35 USC § 112, first paragraph (enablement).

4. Claims 1,4,7,8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

First, the claims address use of "activity prediction formula". Specification does not teach any activity prediction formula; the only formula addressed is the one on Fig. 3. However, neither the activity shown in the table of Fig. 3, nor the terms used in the formula are explained in the specification. It seems from the specification, p. 30, first paragraph, that Fig. 3 addresses function evaluating interactions between the represented point and the molecules, rather than "activity prediction formula" addressed in the claim. As follows from applicant's discussion, p. 17 of the response of 03/19/2009, Fig. 3 demonstrates CoMFA data table, and equation derived therefrom. However, applicant highlights the different nature of the "represented point" as compared to "probe atoms" of CoMFA (p. 13 of the response of 03/19/2009):

> Instead of using a probe atom, the present application directs the use of a represented point, which is a different point of reference within the molecule being analyzed and is determined using a different method when compared to traditional CoMFA

Thus an artisan would not know how to make the invention as claimed without undue experimentation.

Applicant is warned against introducing new matter into specification. Note that none of multiple references addressed throughout specification are incorporated by reference.

Second, with regard to compounds being used for generating a new chemical compound, claims 1,4,7,8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for clustering atoms of compounds having similar structure and subsequent extraction of relevant information from "represented points" generated thereby, do not reasonably provide enablement for generating quantitative structure-activity relationship for a chemical compound derived from a plurality of molecules each having a related biological activity (emphasis added).

The breadth of the claims encompass clustering of molecules that have no common structure with the only similarity being "related biological activity". As the metes and bounds of the term "related biological activity" is not clear and is not defined in specification, as discussed above, the claims address clustering of molecules of unrelated structure. In the example made above, treating blood circulation disorders can considered to be a related biological activity. Consequently, the claims would encompass clustering of such "unrelated" compounds as heparin, blood coagulation proteins, iron salts, and aspirin. Coincidental superposition of atoms of such apparently structurally unrelated compounds would result in generating "represented points" which "represent" coordinates of atoms of potentially unrelated structures. Combination of such arbitrary "represented points" (which are merely 3D coordinates) is unlikely to result in a meaningful chemical compound,

Specification provides working examples for steroids (p.31) or Cox-2 inhibitors (p. 55) – i.e., each group having similar structures. Specification does not provide guidance on how to carry out the method as claimed and generate chemical compounds using compounds which do not have similar structure.

Prior art, for example Cramer et al, or Klebe et al, cited in the instant specification, address QSAR analysis of compounds having similar structure, rather than having only vague related biological activity in common.

In view of the above, it is the Examiners position that with the insufficient guidance and working examples and in view of unpredictability and the state of art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue amount of experimentation.

Response to arguments

There are two enablement rejections that have been made (and maintained) as above. Applicant addresses only the first one.

With regard to the activity prediction formula, the activity prediction formula in the claims is addressed with relation to each **atom** of the putative compound. Fig. 3 does not describe assigning activity value to each atom, rather it addresses "points" which are 3D coordinates in virtualm space. Furthermore, as for paragraph [0009], Fig. 3 describes CoMFA method from which the instant invention distinguishes itself. Further, neither the activity shown in the table of Fig. 3, nor the terms used in the formula are explained in the specification. It seems from the specification, p. 30, first paragraph, that Fig. 3 addresses function evaluating interactions between the represented point and the molecules, rather than "activity prediction formula" addressed in the claim.

Conclusion

7. No claims are allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631

mlb